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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/885,259	02/23/2001	Madhav N. Devalaraja	PC18174A	3713

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Paul H. Ginsburg
Pfizer Inc
Patent Department
235 E. 42nd Street (150-05-49)
New York, NY 10017-5755

EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	10

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,259	DEVALARAJA ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14 and 31-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14 and 31-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed 11/15/02 (Paper No. 9), is acknowledged.

Claims 12, 14 and 31- 44 are pending.

2. Applicant's election of Group XIII, Claims 12, 14, 31-33 (now Claims 12,14 and 31-44) in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 12, 14 and 31- 44 are under consideration in the instant application.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

4. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948. All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

5. Claims 32, 35 and 36 are objected to because both claims being dependent upon themselves . Appropriate correction is required.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 38, 39 and 40 - 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Dependent claims 40 recites "antagonist" and "mCSF". There is insufficient antecedent basis for this limitation in base claims, since base Claim 14 and base claim 12 do not recite "antagonist" and "mCSF".

B). Dependent claim 41 recites "antibody". There is insufficient antecedent basis for this limitation in the base claims, since base Claim 14 and base claim 12 do not recite "antibody".

C). Dependent claims 43 recites "antagonist". There is insufficient antecedent basis for this limitation in the base claim, since base Claim 36 does not recite "antagonist".

D). Dependent claim 44 recites "antibody". There is insufficient antecedent basis for this limitation in the base claims, since base Claim 37 and base claim 31 do not recite "antibody".

E) Dependent claim 38 recites "antagonist". There is insufficient antecedent basis for this limitation in base claims, since base claim 36 does not recite "antagonist".

F). Dependent claim 39 recites "antibody". There is insufficient antecedent basis for this limitation in the base claims, since base Claim 37 and base claim 31 do not recite "antibody".

G). Claim 42 is indefinite and ambiguous in the recitation of " ...treating asthma by administrating mCSF antagonist to treat psoriasis" . It is unclear what disease Applicant intended to treat by administering mCSF antagonist ?

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 12, 14, 31- 44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for: 1) a method for screening for an inhibitors of a CSF and mCSF in vitro assays based on inhibition of chemoattraction and/or accumulation and /or activation of leukocytes by CSF and;2) in vivo recruitment assay response to IL-8, using rabbit as animal model, does not reasonably provide **enablement** for: 1) a method of treating inflammation, such as sepsis, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a CSF, claimed in Claims 12 and 14, or 2) a method of treating inflammation, such as psoriasis or asthma, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a m-CSF, such as antibody, claimed in Claims 31, 32, 37 and 42 or 3) a method of treating rheumatoid arthritis in a mammal comprising administering any mCSF antagonist, such as antibody, claimed in Claims 34 and 35. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the

unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.
The specification only discloses detailed *in vitro* chemotaxis assay , calcium flux assay and binding assay (Example 1 of the Specification as filed), a protocol screening assay for G-CSF receptor antagonists (Example 2 of the Specification as filed) and a protocol screening assays for inhibitors of the synergistic effect of M-CSF on a chemokine-induced, monocytes-mediated inflammation, based on directly measuring activation of human monocytes (Example 3 of the Specification as filed). The specification does not adequately teach how to effectively treat inflammation, including sepsis, rheumatoid arthritis, asthma and psoriasis, by administering an effective amount of inhibitor of a CSF or inhibitor of mCSF. Moreover, no animals were used as model system to effectively treat inflammation in a subject, comprising administering to the subject an effective amount of inhibitor of a CSF. Since there is no animal model system in the specification to effectively treat inflammation by administering to a mammal a therapeutically effective amount of inhibitor of a CSF, it is unpredictable how to correlate *in vitro* results with *in vivo* use. Since the method of treating inflammation, by administering to a mammal a therapeutically effective amount of inhibitor of a CSF and mCSF can be species- and model-dependent (seeVan Noort et al. International Review of Cytology, 1998, v.178, pages 127-204, Table III in particular) , it is not clear that reliance on the *in vitro* studies accurately reflects the relative mammal and human efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of a method of treating inflammation, including sepsis, rheumatoid arthritis, asthma and psoriasis by administering to a mammal a therapeutically effective amount of inhibitor of a CSF or inhibitor of mCSF . Moreover, Applicant himself acknowledge that the ability of CSF to synergistically enhance the chemoattractant effects of chemokines on recruitment of leukocytes to sites of inflammation was unexpected (page 4, line 8 of the Specification as filed) . As such, the invention must be considered unpredictable.

It addition, Campbell et al. (J. of Immunol. 1998, , v.1998, pages 3639-3644) teach that the approaches that used the inhibitors of a CSF or receptor antagonists of the cytokines to develop the methods of treating inflammation have several limitations such as: 1) the inhibitors of CSF, including monoclonal antibody may not be accessible to the site of the action; 2) there may be reduced efficacy of the neutralizing antibody due to an immune response to this foreign protein (see Discussion overlapping pages 3642-3643 in particular).

Moreover, an effective protocol for a method of treating inflammation, is subject to a number of factors which enter the picture beyond simply the administration to the subject an effective amount of an inhibitor of a CSF. Demonstrating *in vitro* chemotaxis assay , calcium flux assay and binding assay (Example 1 of the Specification as filed), a protocol screening assay for G-CSF receptor antagonists (Example 2 of the Specification as filed) and a protocol screening assays for inhibitors of the synergistic effect of M-CSF on a chemokine-induced, monocytes-

mediated inflammation, based on directly measuring activation of human monocytes cannot alone support the predictability of a method of treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis by administering to a mammal a therapeutically effective amount of inhibitor of a CSF or inhibitor of mCSF. Van Noort et al. (International Review of Cytology, 1998) indicate factors that effect immune response such as genetic, environmental and hormonal (Page 176, Paragraph 3). The ability of a host to enhance an immune response will vary depending upon factors such as the condition of the host and burden of disease.

The specification does not provide sufficient teaching as to how it can be assessed that treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis was achieved after the administration of a therapeutically effective amount of inhibitor of a CSF or inhibitor of mCSF. Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method of treating inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis, comprising administering an effective amount of a therapeutically effective amount of inhibitor of a CSF or inhibitor of mCSF in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Also an issue is that the specification does not provide a sufficient enabling description for any antagonist or any inhibitor of a CSF or mCSF to treat inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis.

The claims as written encompass the genus of antagonists or inhibitors of a CSF or mCSF. The genus encompasses peptides wherein such peptides have numerous differences in amino acid sequences.

Applicant discloses only CSF antibodies, as inhibitors of CSF. Applicant has not taught how to make and/or use any antagonist or any inhibitor of a CSF or mCSF to treat inflammation in a subject, including sepsis, rheumatoid arthritis, asthma and psoriasis. The structural and functional characteristics of said antagonist or inhibitor are not defined in the specification or in the claims.

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Applicant is relying upon certain biological activities and the disclosure of a single species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated any antagonists or any inhibitors of CSF or mCSF encompassed by the claimed invention would be expected to have greater differences in their activities.

Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. inhibit CSF or mSCF) requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects the peptides and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to functional proteins or peptides with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of any antagonist or any inhibitor of CSF or mCSF, broadly encompassed by the claimed invention.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, absence of working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 12, 14, 31- 44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of: 1) a method for screening for an inhibitors of a CSF and mCSF in vitro assays based on inhibition of chemoattraction and/or accumulation and /or activation of leukocytes by CSF and ;2) in vivo recruitment assay response to IL-8, using rabbit as animal model.

Applicant is not in possession of: 1) a method of treating inflammation, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a CSF, claimed in Claim 12, or 2) a method of treating inflammation, comprising administering to a mammal a therapeutically effective amount of any inhibitor of a m-CSF, claimed in Claim 31, or 3) a method of treating rheumatoid arthritis in a mammal comprising administering any mCSF antagonist, claimed in Claim 34.

Applicant only discloses detailed *in vitro* chemotaxis assay , calcium flux assay and binding assay (Example 1 of the Specification as filed), a protocol screening assay for G-CSF receptor antagonists (Example 2 of the Specification as filed) and a protocol screening assays for inhibitors of the synergistic effect of M-CSF on a chemokine-induced, monocytes-mediated inflammation, based on directly measuring activation of human monocytes (Example 3 of the Specification as filed) therefore, the skilled artisan cannot envision how to effectively treat inflammation , by administering to the subject an effective amount of any inhibitor of CSF as recited in the instant claims. Applicant does not described how to extrapolate data obtained from *in vitro* studies to the development of effective *in vivo* mammalian including human therapeutic treatment, comprising administering to the subject an effective amount of any inhibitor of CSF commensurate in scope with the claimed invention. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. No claim is allowed.

12. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
January 27, 2003

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600